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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,101	05/18/2001	Robert D. Mass	3118/1H146US1	9233

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EXAMINER	
GODDARD, LAURA B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,101	MASS, ROBERT D.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 26-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/20/04, 11/8/04.* 7/19/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed July 13, 2005 is acknowledged. Claims 27-31 were added. Claims 21 and 26-31 are currently under prosecution.

2. The text of those sections of Title 35, US Code not included in this action can be found in a prior Office Action.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

3. The rejection for claims 21 and 26 under 35 U.S.C. 112, first paragraph, scope of enablement is withdrawn in view of the amendments to the claims.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21, 26-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying and treating a patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, comprising detecting her2 gene amplification in breast cancer tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer, wherein the patient's tumor cells express HER2 at a **2+ or 3+** level by immunohistochemistry, does not reasonably provide enablement for a method for identifying and treating a patient disposed to

respond favorably to HER2 antibody, huMAb4D5-8, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer, wherein the patient's tumor cells express HER2 at a **0 or 1+** level by immunohistochemistry. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to practice the invention commensurate in scope with these claims.

The claims are drawn to a method for identifying and treating a patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, for treating breast cancer, comprising detecting her2 gene amplification and treating the patient with HER2 antibody, wherein the patient's tumor cells express HER2 at a 0 or 1+ level by immunohistochemistry.

The specification discloses the requirement for overexpression of HER2 at the 2+ or 3+ level immunohistochemistry (IHC) for enrollment in the Herceptin® breast cancer trials. The specification also discloses the detection of Fluorescence *In Situ* Hybridization (FISH) positive samples that were included in the Clinical Trials Assay (CTA) negative samples, samples that did not meet the 2+ or 3+ requirement (Example 1). The specification speculates that the identification of FISH+ patients in the 1+ and 0 sub-groups might identify subjects, though failing the IHC criteria for Herceptin® treatment, that would likely benefit from Herceptin® treatment. The specification further discloses a correlation between the FISH status with response to Herceptin® treatment for 2+ and 3+ subjects (Example2), wherein the FISH+ subjects showed a much greater response to chemotherapy and Herceptin® than FISH- subjects, suggesting FISH+

selection analysis in combination with IHC detection of HER2 overexpression provides a more accurate indicator of likelihood of success with Herceptin® treatment than for IHC analysis alone (p. 32). The specification discloses that FISH identifies patients in the 1+ and 0 IHC categories who are excluded from treatment because expression of HER2 is too low for effective therapy (p. 32).

Other than a correlation between FISH+ subjects and 2+ and 3+ IHC subjects who responded favorably to treatment, there is only a hypothesis that 0 and 1+ patients would also benefit from treatment. One cannot extrapolate the teaching of the specification to the scope of the claims because, as drawn to the treatment of breast cancer that does not overexpress HER2, US Patent No. 6,156,321 specifically teaches that among the drawbacks of antibody anti-tumor therapy is that antigen-negative cells can survive and repopulate a tumor (col. 1, line 64; col. 2, line 2). Further, Lewis et al (Cancer Immunology Immunotherapy 37: 255-263, 1993) specifically teach, in Table 2 in *in vitro* studies, that while proliferation of cell lines that over-express ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not over-express ErbB2 was generally unaffected (page 259). Thus, no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed in treating breast cancer that does not overexpress HER2. Successful, effective administration of HER2 antibody to treat breast cancer in 0 and 1+ IHC level patients cannot be predicted based only on the hypothesis provided by the specification. Low expression levels of HER2 at the 0 and 1+ IHC level in a breast cancer patient would suggest a lack of HER2 receptors present, and in the absence or near absence

of receptor, it would not be expected that the antibody would be effective to treat, especially in view of the teaching in the art that effective treatment would not be predictably expected at IHC levels less than 2+ or 3+.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

Note: If applicant were to overcome the preceding rejection (s) under 35 U.S.C. 112, first paragraph, the following claims would still be rejected under 35 U.S.C. 112, first paragraph, scope of enablement:

5. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying and treating a breast cancer patient disposed to respond favorably to HER2 antibody, huMAb4D5-8, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with said HER2 antibody, does not reasonably provide enablement for a method for identifying and treating a patient disposed to respond favorably to HER2 antibody which inhibits cellular proliferation of HER2-overexpressing human breast tumor cells, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to practice the invention commensurate in scope with these claims.

The claims are drawn to a method for identifying and treating a patient disposed to respond favorably to HER2 antibody which inhibits cellular proliferation of HER2-overexpressing human breast tumor cells, comprising detecting her2 gene amplification in tumor cells from the patient and treating the patient with the HER2 antibody to treat the breast cancer. This means the claims are drawn to a method of identifying and treating a patient comprising treating the patient with **any** HER2 antibody. This includes treating with (1) any antibody to HER2 regardless of where it binds on HER2, (2) regardless of whether it cross reacts with other antigens including EDGF receptor, (3) treating with polyclonal antibodies, (4) regardless of whether the antibody is humanized, and (5) regardless of the whether or not the carcinoma cells overexpress HER2 protein.

The specification discloses the successful treatment of cancer patients with HER2 antibody, huMAb4D5-8 or Herceptin® (p. 5, line 22).

One cannot extrapolate the teaching of the specification to the scope of the claims because (1) although the specification claims a method using any antibody to HER2, the specification specifically states that it is Herceptin®, and not any HER2 antibody, which is postulated as a therapeutic strategy for cancer patients with breast cancer overexpressing HER2 (p. 16, lines 3-10). It is clear that it is well known in the art Herceptin® is an effective anti-cancer agent in tumors that overexpress HER2. However, other than stating that this well-known antibody, Herceptin®, is an example of

the claimed antibodies of the invention, the specification does not teach how to make a therapeutic antibody with the properties required for effective treatment of HER2-overexpressing breast cancer so that it will function as claimed. For example, Stancovski, et al (PNAS,USA, 88:8691-8695, 1991) characterized the effects of various antibodies that bind the extracellular domain of ErbB2 upon the growth of tumor cells. Stancovski, et al teach, while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the anti-ErbB2 antibodies actually accelerates tumor growth (page 8693, column 1). This phenomenon was also reported in Lewis, et al (Cancer Immunology Immunotherapy 37: 255-263, 1993). US Patent No. 5,677,171 teaches that not every anti-ErbB2 antibody can be used as effectively as monoclonal antibody 4D5 (col 18, lines 15-23). More specifically, '171 teaches that some anti-ErbB-2 antibodies inhibited growth to a lesser extent than MAb 4D5 while others failed to inhibit growth. Further, Strobel, et al (Gynecologic Oncology 73: 362-367, 1999) teach discordant effects of contacting cancer cells with two different neutralizing monoclonal antibodies, i.e., antibodies that block the function of the receptor protein to which they specifically bind (abstract). Despite the fact that both anti-receptor antibodies had been shown to block ligand binding to the receptor, Strobel et al found that only one of the antibodies could be used effectively to block cancer cell adhesion to inhibit malignancy. Thus, in the absence of guidance on how to make effective antibodies, other than huMAb4D5-8, one could not predictably practice the broadly claimed invention.

Further, clearly one would not expect to be able to practice the claimed invention with an antibody that was not specific for the extracellular domain of HER2, for example

an antibody to the intracellular domain or an antibody that binds only to denatured HER2, because the antibody would not bind to malignant cells expressing ErbB-2, since the antibody could not contact the intracellular domain of the protein, would not be able to bind to a folded protein and therefore would not inhibit the cells growth and/or proliferation. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

As drawn to (2) cross-reactivity of the broadly claimed antibody. It is well known in the art, as taught by Karunagaran et al (EMBO J., 1996, 15:254-264) and Graus-Porta et al (EMBO J., 1997, 16:1647-1655), that HER2 is a member of the EGFR family and shares homology with other members of the family. Given the shared homology it would be expected that antibodies that are not selective for HER2 would cross react with, and be sequestered by, other members of the EGFR family. In particular it is known that anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the anti-tumor antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a

sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the antibody has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

As drawn to (3) polyclonal antibodies. The claim as written read on monoclonal and polyclonal antibodies. As set forth above, given the identity of HER2 with other members of the EGFR family, it would be expected that a large majority of polyclonal antibodies would bind to epitopes that are shared among members of the EGFR family. These sequestered antibodies would not be available to treat the cancer and it could not be predicted, for the reasons set forth above that the broadly claimed method will function as claimed with a reasonable expectation of success using polyclonal antibodies.

As drawn to (4) non-humanized antibodies, Winter et al (TIPS, 1993, 14:139-143) specifically teach that a major problem with the use of murine monoclonal antibodies in the treatment of human subjects is the development of human antimouse antibodies (HAMA) that can inactivate the injected antibodies. Thus, it would be expected that the

injection of cross species antibody would result in anti-other species antibodies and/or cytotoxic T cells against the injected antibody. Further, Baselga et al (J. Clin. Oncol, 1996, 14:737-744) specifically teach that murine antibodies are limited clinically because they are immunogenic. To facilitate clinical investigations, MAb 4D5 (the murine parent antibody of HERCEPTIN) was humanized. The humanization resulted in a safe treatment which has dose dependent pharmacokinetics in phase I clinical trials (p. 737, col 2). Given the teaching in the art, it could not be predicted and it would not be expected that non-humanized antibodies would function as claimed, that is as a therapeutic for the treatment of HER2-overexpressing breast cancer patients that is clearly contemplated.

As drawn to (5), treatment of cancer that does not overexpress HER2 protein, US Patent No. 6,156,321 specifically teaches that among the drawbacks of antibody anti-tumor therapy is that antigen negative cells can survive and repopulate a tumor (col 1, line 64, col 2, line 2). Further Lewis et al, Supra, specifically teach, in Table 2 in *in vitro* studies, that while proliferation of cell lines that over-express ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not over-express ErbB2 was generally unaffected (page 259). Thus, no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed in a cancer that does not overexpress HER2. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which

would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

6. Some of the Applicant's arguments drawn to the previous rejection of claims are relevant to the instant rejection.

Applicant argues that US Patent 5,677,171 discloses several growth inhibitory HER2 antibodies and that growth inhibitory HER2 antibodies could have been made and screened. The argument has been considered but has not been found persuasive because given that the art recognized the unpredictability of treatment with the various HER2 antibodies (see rejection above), one would not be able to predict with a reasonable expectation of success which antibodies would function as claimed. Clearly, Applicant has not taught how to make the broadly claimed HER2 antibody. Applicant argues that one could screen for antibodies to HER2 that function effectively, however the ability to screen does not satisfy the enablement rejection because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicant argues that the mechanism is not required in order to make and use antibodies, other than Herceptin®, that inhibit cellular proliferation. The argument has been considered but has not been found persuasive. Although the mechanism is not required, only a single antibody, Herceptin®, has been taught that effectively and predictably treats HER2 protein overexpressing cancer. This is not sufficient to enable

the claimed invention or to teach how to make the broadly claimed antibody that will function as claimed to effectively treat breast cancer overexpressing HER2.

Applicant argues that there appears to be some HER2 antibodies (e.g. 24C), and points to Agus et al, Cancer Cell, 2002, 2:127-137, that are effective on breast tumors that express normal levels of HER2 and do not overexpress HER2. Applicant argues that there is evidence indicating that HER2 antibodies other then Herceptin® are effective on breast tumors that overexpress HER2. The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted. Further, enablement is required at the time the invention was made and a post filing disclosure of an effective antibody does not provide an enablement for a method applied for on May 19, 2000.

Applicant provides general teachings from the specification for identifying patients and treating patients with growth inhibitory HER2 antibodies. The argument has been considered but has not been found persuasive because the general teachings set forth in the specification do not remedy the lack of enablement drawn to the broadly claimed therapeutic for the reasons set forth above.

Applicant argues that no evidence is provided by the Examiner to show that the correlation between her2 amplification and clinical responses provided by the present application would not pan out for other growth inhibitory HER2 antibodies. The argument has been considered but has not been found persuasive. Although correlation is known between Herceptin® and treatment, at the time the invention was made, no other effective predictable therapeutic was known. Further, the specification does not

provide a correlation between her2 gene amplification and clinical responses in patients with an IHA level of 0 or 1+ to any HER2 antibody, including the well-characterized and effective huMAb4D5-8. The specification provides a hypothesis that treatment with huMAb4D5-8 might be effective for patients with IHC levels of 0 or 1+, which for the reasons set forth above, is not enabling. The Applicant argues that clinical data drawn to Herceptin® can be extrapolated to any anti-HER2 antibody. This is clearly not the case for the reasons set forth above.

7. All other objections and rejections recited in the previous Office Action are hereby withdrawn.

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER